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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,528	09/26/2001	Y. Tom Tang	PF-0701 USA	3765

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,528	TANG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,12,30-45 and 71* is/are pending in the application.

4a) Of the above claim(s) *1,12,30,33,35,44,45 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,31,32,34 and 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4&11* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 2/12/03 (Paper No. 12), is acknowledged.

2. Claims 1, 11-12, 30-45 and 71 are pending.

3. Claims 1, 12, 30, 33, 35, 44, 45 and 71 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 11, 31, 32, 34, and 36-43 are under examination.

5. Examiner acknowledgment the PCT/US00/13975 application, filed May 19, 2000 and agreed with the Applicant that Applicant is not required to provide a certified copy of a PCT filed with the USPTO.

6. In view of the amendment filed on 2/12/03, paper No. 10, only the rejections set forth below are remained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 36-41 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "specificity" recited in claim 36, line 1 and claim 39, line 1 is ambiguous and unclear and the metes and bounds of the claimed "specificity" is not defined.

Applicant argue that the specification on page 23, line 27 provides a definition for the term "specificity" wherein "specific binding" and "specifically binding" refer to the interaction between a protein or peptide and an agonist, an antibody, and antagonist, a small molecule, or any natural or synthetic binding composition. Applicant further argues that the definition of "specificity" in a basic text on Immunology, Kuby is defined as the capacity of antibody and T-cell receptor to recognize and interact with a single, unique antigenic determinant.

However, it is well known in the art that every antiserum has a different specificity because the repertoire of antibodies produced by animal is somewhat different. Thus, it is unclear one skill in the art would be able to make an antibody with the specificity of the antibody to SEQ ID NO:16.

9. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

10. Claims 11, 31, 32, 34 and 36-43 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility essentially for the same reasons set forth in the previous Office Action, paper No. 8, mailed 8/13/02.

Applicant's arguments, filed 2/12/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicant argues the invention has specific utility because (a) that the antibodies to SEQ ID NO:16 can be used to diagnose islet cell tumors, (b) SEQ ID NO: 16 has homology to pancreatic polypeptide and it is known that the presence of pancreatic polypeptide is a marker for islet cell tumors, the Examiner's attention is drawn to table 2 to demonstrate the homology of SEQ ID NO: 16 to gp190270, including signature sequence for the signal, pancreatic hormone peptide and precursor motifs. Further, Applicant argues in conjunction with Adrian *et al* 1986 and Bordi *et al*, 2002, that it is known that high circulating levels of pancreatic hormone peptide are diagnostic of certain tumors of the pancreas. Applicant further argues in conjunction with IBL Immuno-Biological Laboratories radio-immuno assay kit the diagnostic tests which are commercial available demonstrate "real world" credible use. Applicant concludes that because the demonstrated homology between SEQ ID NO: 16 and pancreatic polypeptide, as well as the demonstrated selective production of SEQ ID NO: 16 in islet cells and islet tumors, a specific and substantial, and credible utility for anti-SEQ ID NO: 16 antibodies is provided by the specification.

While Adrian et al, Bordi et al, and IBL Immuno-Biological Laboratories radio-immuno assay kit provide support for the use of antibodies against pancreatic peptides as a diagnostic test for such tumor wherein the peptide is elevated. Applicants based their conclusion only on a sequence homology, further applicants' specification lack information regarding a correlative or causal relationship between the secreted polypeptide normal islet cells and the tumor islet cell. Furthermore, as indicated in the previous office action that Leiter et al (J Biol Chem 260:13013-13017, 1985) indicate that using Southern blot analysis of SEQ ID NO: 42 homolog, the gene detected in a pancreatic polypeptide-producing islet cell tumor was indistinguishable from that in normal human leukocytes. Therefore, it is unclear whether the one skilled in the art would be able to distinguish between the secreted polypeptide from islet cell, islet cell tumor and the normal human leukocytes or combination thereof in the diagnostic test.

Applicant argues that the Examiner used Leiter et al, reference to assert pancreatic-polypeptide can be expressed in non-islet cells, although both normal and tumor islet cells express pancreatic polypeptide, this does not take away from the utility of the invention as claimed. Applicant further argues that Adrian et al, discusses plasma concentration of pancreatic polypeptide as a

marker for pancreatic endocrine tumors, wherein in atropine suppression can be used to distinguish normal secretion from tumor-related secretion of pancreatic polypeptide.

However, It is unclear how would one skilled in the art employ a diagnostic assay for islet tumor cell using SEQ ID NO: 16 as a marker because SEQ ID NO:16 is different form the pancreatic polypeptide (PP) taught by Adrian *et al.* Further, the specification has not established a correlative relationship between the normal and tumor islet cells.

Applicant argues in conjunction with Bonneau *et al* and Brenner *et al* that homology to sequences of known function is a commonly used and reliable techniques in the art for elucidating function. Applicant reached the conclusion that functional determinations where there is sequence homology to known structures and where known motifs have been identified is not presumptuous.

However, as mentioned in the previous office action Skolnick *et al.* (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 11, 31, 32, 34, and 36-43 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to used the claimed invention for the same reasons set forth in the previous Office Action, paper No. 8, mailed 8/13/02.

Applicant's arguments, filed 2/12/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicant argues that the specification, example XIII at page 62, line 31 provides sufficient disclosure to enable the production of specific antibodies raised against specific antigens. Applicant further asserts that one of skill in the art is fully enabled to produce an antibody that recognizes the specific antigens listed in the claims.

Applicant arguments are found compelling however, Applicant did not address the fundamental bases of the rejection. There is insufficient guidance and direction as to how to make any polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO: 16; any biologically active fragment wherein the fragment having at least 90% identity with the amino acid sequence of SEQ ID NO: 16 and in turn make antibodies which specifically binds to those polypeptide.

13. Claims 11, 31, 32, 34 and 36-43 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action, paper No. 8, mailed 8/13/02.

Applicant's arguments, filed 2/12/03 (Paper No. 10), have been fully considered, but have not been found convincing.

Applicant argues that USPTO written Description Guidelines referenced by the Examiner provides that it is well known that antibodies can be made against virtually any protein, further, the example provides that the antibody is a mature technology where the level of skill is high and advanced. Applicant further asserts that the specification has provided sequence data for the peptide antigen and structural information relating thereto.

However, there is no described or art-recognized correlation or relationship between the structure of the invention, the SEQ ID NO: 16 and expression in islet and islet tumor cells, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of the polypeptides with at least 90% identical to the amino acid sequence of SEQ ID NO: 16 which retain the features essential to the instant invention.

14. The new grounds of rejections are set forth herein, the new grounds of rejections are necessitated by the amendment filed on 2/12/03, paper No. 10.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 11, 37, 40 and 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan and the known fact disclosed in the specification on Table 2, 2nd row.

Adrian *et al* teach rabbit antibody to human pancreatic polypeptide (see page 288, left column, 3rd paragraph in particular). Although Adrian et al do not teach specific amino acid sequence of SEQ ID NO: 16, the amino acid sequence of pancreatic polypeptide, binding to "SEQ ID NO: 16" is considered an inherent property of the reference antibodies.

As is evidenced in the specification on Table 2, row 2, that the human pancreatic polypeptide is the claimed SEQ ID NO:16.

Further, as is evidenced by Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, mean that "specifically bind" with both proteins and still specific. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

Similarly, Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

Claims 37, 40 and 42-43 are included because an antibody is the same antibody irrespective how it is made.

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:16 recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

18. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan and the known fact disclosed in the specification on Table 2, 2nd row as in view of Owens *et al* (1994).

The teachings of Adrian *et al* and the evidentiary references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody in claim 31.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Adrian et al as chimeric, humanized antibody, Fab and $F(ab')_2$ fragments taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan and the known fact disclosed in the specification on Table 2, 2nd row in view of Bird *et al* (1988).

The teachings of Adrian *et al* and the evidentiary references, have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a single chain antibody in claim 31.

Bird *et al* teach a single chain antigen binding proteins composed of an antibody variable light – chain amino acid sequence (V_L) tethered to a variable heavy –chain sequence (V_H) by a designed peptide that links the carboxyle terminus of the V_L sequence to the amino terminus of the V_H sequence. Bird *et al* further teach that the single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion (see the entire document and page 426, left column, 2nd paragraph in particlular)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Adrian et al as a single chain antibody as taught by the Bird *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because single chain antibodies have significant advantages over monoclonal antibodies in a number of applications such as lower back ground in imaging applications since the single chain antibody lack the Fc portion as taught by Bird *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Claims 36 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan and the known fact disclosed in the specification on Table 2, 2nd row in view of Harlow (1989).

Adrian et al. and evidentiary references have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a method of making polyclonal/monoclonal antibody in claims 36 and 39.

Harlow *et al* teach a method of producing polyclonal antibody to any antigen (see entire document and page 96, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. In addition, Harlow et al teach a method of producing monoclonal antibodies comprising immunizing an animal (i.e. a mouse) with a protein or portion thereof (i.e. fragments), harvesting spleen cells from said animal, fusing said spleen cells with myeloma cell line, and culturing said fused cells (i.e hybridoma) under conditions that allow production of said antibody. Harlow et al further teach that the monoclonal antibodies stems from their specificity, homogeneity and ability to be produced in unlimited quantities (see pages 141-157 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce both polyclonal and monoclonal antibody using the method taught by Harlow *et al* with the pancreatic polypeptide as taught by Adrian *et al.*

One ordinary skill in the art at the time the invention was made would have been motivated to make do so because Harlow *et al* teach rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* further teach a method of producing polyclonal antibody to any antigen (See page 96, in particular). Further, One ordinary skill in the art at the time the invention was made would have been motivated to make monoclonal antibody against pancreatic polypeptide because the monoclonal antibodies produced exhibit a high degree of specificity and great affinity as taught by Harlow et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. Claims 32, 34, 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian *et al* (IDS Ref. A) as is evidenced by Bost *et al,* Bendayan and the known fact disclosed in the specification on Table 2, 2nd row in view of U.S. Patent No. 5,766,910.

Adrian *et al* reference and the evidentiary references have been discussed, supra. Adrian et al further teach that the release of pancreatic polypeptide from normal cells has been shown to be under cholinergic control and is inhibited by atropine, whereas the secretion of pancreatic polypeptide from a tumor may be expected to be autonomous (see page 287, right column, middle paragraph in particular). Adrian et al concluded Atropine suppression test can be useful in either confirming the presence of a tumor secreting pancreatic polypeptide or excluding it in patients with moderate elevations of circulating pancreatic polypeptide (see page 291 last paragraph in particular).

The claimed invention differs from the reference teaching only by the recitation of a composition comprising the antibody and an acceptable excipient in claims 32, 38 and 41, a composition wherein the antibody is labeled in claim 34.

The '910 patent teaches the use of antibodies in detection can be in vitro as in a diagnostic assay of a sample obtained from a subject or in vivo. When administered in vivo, the antibodies can be administered as a pharmaceutical composition comprising the antibody and a pharmaceutically acceptable carrier. Immunological procedures useful for in vitro detection of a target a protein or peptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include serum diagnostic assays. An antibody can be labelled so as to be detectable using various methods. For example, a detectable marker can be directly or indirectly attached to the antibody. (column 12, lines 5-20 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the antibody to human pancreatic polypeptide taught by the Adrian et al reference in a composition with a pharmaceutically acceptable carrier taught by the '910 patent and further label the antibody taught by Adrian et al as taught by the '910 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such composition can be useful for in vitro detection of a target a protein or peptide in a sample include immunoassays that employ a detectable antibody. Such immunoassays include serum diagnostic assays as taught by the '910 patent and further labeled antibodies can be used as a detectable marker as taught by `910 patent. Such diagnostic assay can be used with Atropine suppression test to confirming the presence of a tumor secreting pancreatic polypeptide or excluding it in patients with moderate elevations of circulating pancreatic polypeptide as taught by Adrian et al.

Form the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. No claim allowed

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
March 24, 2003

Pat J. Nolan
PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
3/24/03